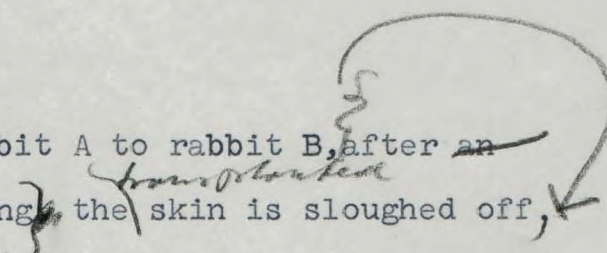


January 30, 1957

On the Possibility of Demonstrating
Desoxyribonuclease-Produced "Transformation"
in Mammals.

By Leo Szilard

If skin is transplanted from rabbit A to rabbit B, after an ^a ~~initial~~ period of apparent healing, ^{transplanted} the skin is sloughed off, 
If subsequently another skin transplant is made from rabbit A to rabbit B, this second skin transplant does not survive as long as does the first transplant. We may express this fact by saying that the first transplant has induced "intolerance" in rabbit B against some "intolerance-producing substances" of rabbit A, to which we shall refer, somewhat sloppily, as "antigens", in quotes. What is the nature of these "antigens"?

It has been recently shown by Billingham, Brent and Medawar⁽¹⁾ that intolerance against skin of a strain ^A of mice can be induced in mice of strain CAB by injecting into CAB mice extract made from ^{spleen} cells of ~~A~~ mice, and they have further shown that the active agent in these cell extracts is destroyed by desoxyribonuclease. The authors have interpreted this phenomenon by assuming that the "antigens" which are responsible for producing intolerance - ^{when} ~~if~~ intolerance is induced by a ~~second~~ skin transplant from rabbit A to rabbit B - are substances that are destroyed by desoxyribonuclease, and are therefore presumably nucleoproteins or nucleic acids. *They write*

Footnote:

"So far as we are aware, only one hypothesis can accommodate these findings: that the antigenic substances responsible for skin transplantation immunity are desoxyribonucleoproteins endowed with antigenic and therefore with genetic specificity."

To me, however, it appears more likely that the observation here quoted must be interpreted in an entirely different way, which is as follows: The cell extract prepared from spleen cells of A mice (in which the active agent can be destroyed by the addition of desoxyribonuclease) induces intolerance in CAB mice against a subsequent skin transplant from mice not because this extract contains the relevant antigens of A mice but rather because this extract is capable (through a process analogous to bacterial transformation) of causing a certain number of cells of injected CAB mice to produce the relevant antigens of A mice.

(1) Dr. R. E. Billingham, Dr. R. Brent and Professor P. B. Medawar, F.R.S., Nature, Vol. 178, p. 514 (1956).

Because of the need to be able to choose between

~~In an attempt to distinguish between the explanation here presented and the explanation given by Billingham, Brent and Medawar, one is led to raise the following question: If intolerance is induced by a skin transplant from an individual A to an individual B (men, mice, or some other suitable species), is thereby delayed hypersensitivity established in B against "antigens" of A in the sense that ^{an injection of a suitably} if an extract of cells A ~~are injected~~ into the skin of B ^{will evoke characteristic skin} one obtains the reaction. If this is, indeed, the case, ^{then we have a test that permits us} one should be able then to distinguish between ~~the~~ two explanations, ^{by} performing this skin test for delayed hypersensitivity on the one hand with that fraction of the extract from cells of A which contain nucleic acid and nucleoproteins, and on the other hand with a fraction which contains no nucleic acid or nucleoproteins (having been treated with desoxyribonuclease).~~

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→ If the explanation of Billingham, Brent and Medawar is correct we should ^{then} expect that an extract prepared from cells A, which contains the nucleoproteins and nucleic acids and which has been treated with proteolytic enzymes, should be able to evoke a skin reaction, but the same extract, after treatment with desoxyribonuclease, should no longer be able to evoke the skin reaction.

~~In the measure in which the experimental evidence available forces us to believe that the observations reported by Billingham, Brent and Medawar are based on transformation, ^{At present one is} one is impelled to look for ^{of a different sort} additional proof that indeed transformation can be accomplished in mammals by the injection of desoxyribonuclease or nucleoproteins. And thus one is ~~led~~ led to consider the possibility of the following experiment:~~

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